AWARD NUMBER: W81XWH-15-1-0645

TITLE: A POC Clinical Trial for PTSD with a First-In-Class Vasopressin 1a Receptor Antagonist

PRINCIPAL INVESTIGATOR: Neal G. Simon, Ph.D.

CONTRACTING ORGANIZATION: Azevan Pharmaceuticals, Inc.
Bethlehem, PA 18015

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
Simon, Neal G., Ph.D.
Difede, JoAnn, PhD

E-Mail: ngsimon@azevan.com

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Azevan Pharmaceuticals, Inc.
116 Research Drive
Bethlehem, PA 18015

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

In this reporting period, year 2 of the project, the major milestones met included obtaining renewal from the responsible local Institutional Review Board (IRB) and the Human Research Protections Office (HRPO) and the DSMB. Patient enrollment began in year 2 with 10 patients currently randomized. In the third year of the project, the major objective will be to continue to recruit and enroll subjects to participate in the clinical study that will test the effect of SRX246, a first-in-class vasopressin 1a receptor antagonist, as a potential new treatment for PTSD.

15. SUBJECT TERMS

PTSD; SRX246; Vasopressin 1a receptor antagonist; Phase II proof of concept clinical trial

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	9	**19b. TELEPHONE NUMBER** *(include area code)*

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1. INTRODUCTION:

The project will test the clinical efficacy of a novel, first-in-class vasopressin 1a receptor antagonist, SRX246 (160 mg PO BID), as a new treatment for PTSD in an 18-week double-blind crossover design Proof-of-Concept Clinical Trial in 42 PTSD patients. In addition, the study also will test in PTSD patients i) the safety and tolerability of SRX246 (160 mg PO BID) and ii) the clinical benefit of SRX246 for the treatment of anger, irritability, and aggression; major depression; disturbed sleep; and quality of life that frequently accompany PTSD.

2. KEYWORDS:

PTSD; SRX246; Vasopressin 1a receptor antagonist; Phase II proof of concept clinical trial

3. ACCOMPLISHMENTS:

***The primary goal* is to provide the initial determination of the clinical efficacy of a novel, first-in-class vasopressin 1a receptor antagonist, SRX246 (160 mg PO BID), as a treatment for PTSD in an 18-week double-blind crossover design Proof-of-Concept Clinical Trial in 42 PTSD patients that compares outcomes in drug vs. placebo arms**

***There are several secondary goals.* These include providing determinations in PTSD patients of the i) the safety and tolerability of SRX246 (160 mg PO BID) and ii) clinical benefit of SRX246 for the treatment of major depression, anger, irritability, and aggression, disturbed sleep, and quality of life that frequently accompany PTSD.**

In this reporting period, year 2 of the project, our major milestones were to obtain local IRB renewal; local DSMB renewal; HRPO renewal; hire and train personnel; and begin the clinical trial study. Our progress and accomplishments are shown below.

Major milestones met during this reporting period are shown in the table below

Major Task 1: Study set-up	Date Completed/Status
Milestone Achieved: Local IRB renewal at WCMC	Completed 2Dec2016
Milestone Achieved: DSMB renewal	Completed 23Jun2017
Milestone Achieved: HRPO renewal	Completed 29Jan2017
Milestone Achieved: Personnel hired and trained,	Completed 09Sept2016
Milestone Achieved: First patient enrolled	Completed 16Dec2016

Weill Cornell Trainings:

- **Held several meetings for establishing policies and procedures manual at local site and training relevant personnel**
- **Several trainings in local data management system REDCap**
- **Additional assessors trained in protocol assessment.**

How were the results disseminated to communities of interest? **Nothing to report**

During the remainder of 2017 and the first quarter of 2018 we expect to:

a. **Continue participant enrollment (Q4 ’17)**
b. **Continue and expand recruitment activities (Q1 ’18)**
c. **Apply for and receive approval for IRB and DSMB Continuing Review (Submission October 2017)**

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report

What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report. **However, this grant was made to Azevan Pharmaceuticals, a small company, thus the technology is already in the private sector**.

What was the impact on society beyond science and technology?
Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Subject accrual into protocol has been slower than anticipated during this report period. This was at first due to slow response to advertisement, which prompted us to greatly expand our advertising efforts (including online postings and print advertisements) over the past two quarters. While these efforts have been successful in generating new study contacts (a total of 190 study contacts have been made thus far), there has been a high number of medical exclusions among individuals recruited through these additional streams. As such, we will continue to try to recruit subjects through new methods, while maintaining our otherwise successful efforts. Specific new methods include greater staff presence at veterans’ events and outpatient medical clinics as well as continued efforts to generate direct referrals from colleagues.

Changes that had a significant impact on expenditures
Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to Report

6. PRODUCTS:

• Publications, conference papers, and presentations
Simon, et al: SRX246: A First-In-Class Vasopressin 1a Receptor Antagonist in Phase II Trials for Mood and Behavioral Disorders. American Society for Clinical Psychopharmacology, Miami, May 2017.

• Website(s) or other Internet site(s)
Nothing to Report.

• Technologies or techniques

Nothing to Report.

• Inventions, patent applications, and/or licenses

Nothing to Report. The technology covering SRX246 was already patented.

• Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Azevan Pharmaceuticals, Inc. Personnel:

Name:	**Neal Simon**
Project Role:	**PI**
Nearest person month worked:	**2**
Contribution to Project:	**Responsible for assuring that specific aims and technical objectives are met in coordination with co-PI and Site-PI**
Name:	**Michael Brownstein**
Project Role:	**co-PI**
Nearest person month worked:	**2**
Contribution to Project:	**Works with PI and Site-PI to assure that specific aims and technical objectives are met**
Name:	**Eve Damiano**
Project Role:	**Regulatory and drug development efforts**
Nearest person month worked	**2**
Contribution to Project:	**Prepares documents for FDA submission, coordinates all drug development tasks, reviews and contributes to protocol development and adherence**
Name:	**Debra Itzkowitz**
Project Role:	**Operations Manager**
Nearest person month worked:	**2**
Contribution to Project:	**supports PI, co-PI, and regulatory and drug development processes, maintains budget and coordinates financial transactions**
Name:	**Margaret Altemus, MD**
Project Role:	**Medical Monitor; hired as an independent consultant**
Nearest person month worked:	**1**
Contribution to Project:	**Responsible for monitoring and evaluation of adverse events and other safety aspects**
Name:	**Lisa Spielman, PhD**
Project Role:	**Statistician; hired as an independent consultant**
Nearest person month worked:	**1**
Contribution to Project:	**Provides data management, evaluation planning, and statistical analysis**

Weill Cornell Personnel

Name:	**JoAnn Difede, Ph.D.**
Project Role:	**PI**
Nearest person month worked:	**3**
Contribution to Project:	**Responsible for assuring that specific aims and technical objectives are met in coordination with co-PIs and Site-PIs**
Name:	**Nancy J. Needell, M.D.**
Project Role:	**Co-I, study physician**
Nearest person month worked:	**1**
Contribution to Project:	**Responsible for the medical evaluation of all patients**
Name:	**James H. Kocsis, M.D.**
Project Role:	**Co-I, study physician**
Nearest person month worked:	**1**
Contribution to Project:	**Responsible for the medical evaluation of all patients**
Name:	**Andrew McAleavey, Ph.D.**
Project Role:	**Co-I, Study assessor**
Nearest person month worked:	**5**
Contribution to Project:	**Responsible conducting all study clinical assessments**
Name:	**Adina Jick**
Project Role:	**Research Assistant**
Nearest person month worked:	**12**
Contribution to Project:	**Responsible for all aspects of the study management including recruitment, scheduling, and data management**

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?
Organization Name: **Weill Cornell Medical College**
Location of Organization: **New York, New York**
Partner's contribution to the project (identify one or more):

Collaboration:

What were the major goals and objectives of the project?

- **Work with Weill Cornell Medical College Clinical and Translational Sciences Center outpatient laboratory to assess participants**
- **Gain local IRB approval**
- **Hire and train additional assessors**
- **Begin recruitment activities following IRB and HRPO approvals**

What was accomplished under these goals?

- **Work with Weill Cornell Medical College to assess participants**

    - **Successfully collaborated with Clinical and Translational Science Center (CTSC) at Weill Cornell to assess patients using blood draws and physical examinations for duration of report period.**
    - **Successfully collaborated with Weill Cornell's research pharmacy to dispense medication and randomize participants throughout report period**
    - **Retained Dr. Erica Jones as study cardiologist to read and evaluate electrocardiogram (ECG) results Gain local IRB approval**
    - **Gained IRB approval on December 2, 2016 for continuing review**
    - **An amendment was submitted to the local IRB on January 17, 2017 and was approved on January 23, 2017**
    - **An amendment was submitted to the local IRB on March 29, 2017 and was approved on April 19, 2017**
    - **An amendment was submitted to the local IRB on June 3, 2017 and was approved on June 27, 2017**
    - **An amendment was submitted to the local IRB on August 2, 2017 and was approved on August 8, 2017**
    - **An amendment was submitted to the local IRB on September 21, 2017 and was approved on September 29, 2017**
- **Hire and train additional assessors**
    - **Drs. Amy Rubenstein, Melissa Peskin, and Colleen Becket-Davenport were successfully trained to conduct study assessments, providing additional availability for participant recruitment.**
- **Continue recruitment activities**
    - **As of 9/25/17, 172 potential participants inquired about the PTSD drug study. Following their initial inquiry, 18 were unable to be contacted again and 37 are still being actively recruited for the study. 117 of the potential participants who inquired about the study were offered the study. After hearing briefly about the study, 21 potential participants were ruled out and 12 declined to participate. 83 potential participants were screened by phone. Following the phone screen, 21 potential participants were ruled out, 5 declined to participate, and 4 were unable to be contacted again. 20 potential participants are scheduled for baseline assessments. 24 potential participants were assessed in person.**
- **See above section for details on trainings and professional development at Weill Cornell site such as trainings in data management system, electronic medical records system, and policies and procedures.**

8. SPECIAL REPORTING REQUIREMENTS: **QUAD CHART: See attached.**

9. APPENDICES: **None**

A POC Clinical Trial for PTSD with a First-In-Class Vasopressin 1a Receptor Antagonist
Log #13077001
Award W81XWH-15-1-0645

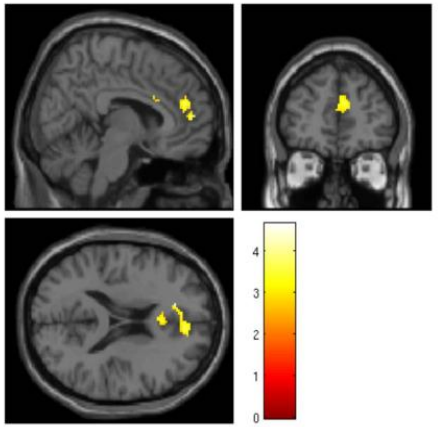
PI: Neal G. Simon, Ph.D. **Org:** Azevan Pharmaceuticals **Award Amount:** $1,577,905

Study/Product Aim(s)

- *Aim 1*: provide the initial determination of the clinical efficacy of SRX246 (160 mg PO BID) as a treatment for PTSD in a 18-week, randomized, double-blind crossover design Proof-of-Concept Clinical Trial in 42 PTSD patients that compares outcomes in drug vs. placebo arms
- *Aim 2*: provide determinations in PTSD patients of the i) safety and tolerability of SRX246 (160 mg PO BID) and ii) clinical benefit of SRX246 for the treatment of major depression; anger, irritability, and aggression; disturbed sleep; and quality of life that frequently accompany PTSD.

Approach

We propose to test the *primary hypothesis* that daily oral treatment with SRX246 will result in clinical improvement in PTSD patients based on changes in CAPS score. *Secondary hypotheses*, including the effect of SRX246 on safety and several quality of life measures, also will be tested.



BOLD activity (Placebo > SRX246; yellow) in anterior cingulate and medial prefrontal cortex. SRX246 treatment significantly attenuated BOLD activation following intranasal AVP ($p<0.005$). Comparable attenuation of BOLD signal was seen in amygdala and temporal parietal junction, regions integral to the processing of social and emotional stimuli.

Accomplishments: 1) IRB and HRPO Renewall Secured 2) Dr. Neal Simon, PI, attended and presented at the MOMRP PTSD Biomarker IPR 3) American Society for Clinical Psychopharmacology Poster

Timeline and Cost

Activities	CY15	CY16	CY17	CY18
Study Set Up				
Randomized Control Trial				
Data Analysis				
Dissemination				
Estimated Budget ($K)	**$103,186**	**$628,379**	**$288,013**	**$548,327**

Goals/Milestones

CY15 Goal – *Study Set Up*
☑Execute Clinical Trial Agreement; Finalize Protocol and submit to IRB

CY16 Goals – *Study Set Up and Randomized Control Trial*
☑Cornell IRB Approval; ☑ Establish Data Safety Monitoring Board
☑ Appoint Independent Medical Monitor; ☑ Recruit Study Physician
☑ HRPO Approval; ☑ Site Initiation Visit ☑ Begin patient enrollment

CY17 Goal – *Randomized Control Trial*
☑Screen, randomize patients, execute protocol tasks over 18 weeks
☑Cornell IRB renewal ☑ DSMB renewal ☑ HRPO renewal

CY18 Goal – *Randomized Control Trial and Data Analysis*
☐ Cornell IRB renewal ☐DSMB renewal ☐HRPO renewal
☐Continue to Screen, randomize patients, execute protocol
☐Database lock, unblinding, completion of analyses
☐Dissemination of findings

Comments/Challenges/Issues/Concerns

- Recruitment and retention delayed timeline
- No Cost 12 month extension approved

Budget Expenditure to Date
Projected Expenditure: $1,577,905 Actual Expenditure: $1,019,577

Updated: October 27, 2017